10/089039 ,092302

JC20 Rec'd PCT/PTO 25 MAR 2002

10/089039

Practitioner's Docket No. 81847

CHAPTER II

Preliminary Classification:

Proposed Class:

Subclass:

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.' " M.P.E.P., § 601, 7th ed.

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/DE00/03441 — INTERNATIONAL APPLICATION NO.

22 September 2000 — INTERNATIONAL FILING DATE

24 September 1999 — PRIORITY DATE CLAIMED

1-AZIRIDINO-1-HYDROXYIMINOMETHYL-DERIVATE, VERFAHREN ZU DEREN HERSTELLUNG UND DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL
TITLE OF INVENTION

IVARS KALVINS, VIKTOR ADRIANOV, IRINA SHESTAKOVA, IVETA KANEPE AND ILONA DOMRACHEVA
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231

ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date March 25, 2002, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL919996088US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

EDWARD M. KRIEGSMAN
(type or print name of person mailing paper)

Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing—See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
☐*	TOTAL CLAIMS	11 −20=	0	× $18.00=	$ 0
	INDEPENDENT CLAIMS	3 −3=	0	× ~~$76.00~~ $84 =	0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ ~~$260.00~~ $280	$280
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 ☒ U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $690.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 ☒ where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) ..... ~~$840.00~~ $890				$890
				Total of above Calculations	= $1170
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				− 585
				Subtotal	585
				Total National Fee	$ 585
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				0
TOTAL				Total Fees enclosed	$ 585

Applicant is a small entity

*See attached Preliminary Amendment Reducing the Number of Claims.

i. ☒ A check in the amount of $585 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

***WARNING:** *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____.
Date

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____.
Date

d. ☒ will follow.

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5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on (date) _____.
Date

c. ☒ have not been transmitted as

i. ☒ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): March 27, 2001

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☐ Annex(es) to the international preliminary examination report

a. ☐ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☐ A translation of the annexes to the international preliminary examination report

a. ☐ is transmitted herewith.

b. ☐ is not required as the annexes are in the English language.

10. ☒ An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____.
Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

c. ☒ will follow.

II. Other document(s) or information included:

11. ☒ An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. ☒ is transmitted herewith.

b. ☐ has been transmitted by the International Bureau.
Date of mailing (from form PCT/IB/308): _____.

c. ☐ is not required, as the application was searched by the United States International Searching Authority.

d. ☐ will be transmitted promptly upon request.

e. ☐ has been submitted by applicant on _____.
Date

12. ☐ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

a. ☐ is transmitted herewith.

Also transmitted herewith is/are:

☐ Form PTO-1449 (PTO/SB/08A and 08B).

☐ Copies of citations listed.

b. ☐ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

c. ☐ was previously submitted by applicant on _____.
Date

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

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14. ☐ Additional documents:

a. ☐ Copy of request (PCT/RO/101)

b. ☐ International Publication No. _____

i. ☐ Specification, claims and drawing

ii. ☐ Front page only

c. ☐ Preliminary amendment (37 C.F.R. § 1.121)

d. ☐ Other

_____

_____

_____

15. ☒ The above checked items are being transmitted

a. ☒ before 30 months from any claimed priority date.

b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

_____

_____

_____

_____

_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 11-1755.

☒ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

☐ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☐ 37 C.F.R. § 1.17 (application processing fees)

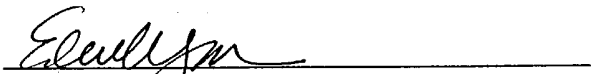
☐ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☐ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).



SIGNATURE OF PRACTITIONER

Reg. No.: 33,529

EDWARD M. KRIEGSMAN

Tel. No.: (508) 879-3500

(type or print name of practitioner)

KRIEGSMAN & KRIEGSMAN
665 FRANKLIN STREET

Customer No.: 23685

P.O. Address

FRAMINGHAM, MA 01702

PATENT
Attorney Docket No. 81847

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
IVARS KALVINS ET AL.	)	
	)	
Serial No.: 10/089,039	)	Group Art Unit: Unknown
	)	
Intl. Appl. Filing Date: Sept. 22, 2000	)	Examiner: Unknown
	)	
For: 1-AZIRIDINO-1-HYDROXY-IMINOMETHYL DERIVATIVES, METHODS FOR PREPARING THEM, AND DRUGS CONTAINING THESE COMPOUNDS	)	

Box PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination of the above-identified patent application, please enter the amendment below.

IN THE CLAIMS:

Please amend claim 4 as follows:

4. (Amended) 1-Aziridine-1-hydroxyiminomethyl derivatives pursuant to claim 1, characterized by the fact that R_1 and R_2 independently of one another represent hydrogen atoms or a $-CONH_2$ group.

REMARKS

No claims have been canceled or added herein. Claim 4 has been amended herein. Therefore, claims 1-11 are under active consideration.

It is respectfully submitted that the present application is in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: _____

Edward M. Kriegsman
Reg. No. 33,529
665 Franklin Street
Framingham, MA 01702
(508) 879-3500

Dated: August 20, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box PCT, Commissioner for Patents, Washington, D.C. 20231 on August 20, 2002

_____

Edward M. Kriegsman
Reg. No. 33,529
Dated: August 20, 2002

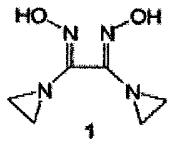
MARKED-UP AMENDED CLAIM 4

4. (Amended) 1-Aziridine-1-hydroxyiminomethyl derivatives pursuant to [one of the preceding claims] claim 1, characterized by the fact that R_1 and R_2 independently of one another represent hydrogen atoms or a $-CONH_2$ group.

1-Aziridino-1-hydroxyiminomethyl Derivatives, Methods for Preparing Them, and Drugs Containing These Compounds

This invention relates to 1-aziridino-1-hydroxyiminomethyl derivatives, methods for preparing them, and drugs containing these compounds.

Only one bis(aziridine oxime) of Formula 1 is known so far in the state of the art (Andrianov, V.G., Eremeev, A.V., Zh. Org. Khim (1991), 27, 112-16; Eremeev, A.V., Piskunova, I.P., Andrianov, V.G., Liepins, E., Khim. Geterotsikl. Soedin (1982), (4) 488-94; Musluoglu, E., Ahsen, V., J. Chem. Research (S) (1999), 142-143).



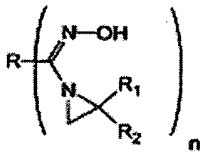
1

Nothing has yet been reported about the biological properties of this compound 1,1'-[1,2-bis(hydroxyimino)-1,2-ethanediyl]bisaziridine (1) or of its use as a drug.

Monoaziridine oximes that are used as herbicides, among others, are also known from DE-OS [Unexamined] 2,132,598. In the same way, aziridine oximes that are used to treat illnesses associated with the function of the chaperone system

are described in WO 97/16439. However, nowhere have bis-, tris-, or even tetraaziridine oximes been described.

The object of this invention is to make available new 1-aziridino-1-hydroxyiminomethyl derivatives with the general formula I



I

and a method for preparing them. Another object is to make available drugs that contain a compound with the general formula I.

In the general formula I, R stands for any organic residue that is able to bond covalently two aziridine oxime groups,

R_1 and R_2 independently of one another stand for a hydrogen atom or a $-CH_3$, $-C_2H_5$, -CN, -COOH, $-COOCH_3$, $-COOC_2H_5$, $-CONH_2$, or $-C_6H_5$ group, and n is the whole number 2.

It is preferred for R to be selected from a single bond, linear or branched, saturated or unsaturated alkanes or heteroalkanes with up to 6 carbon atoms

and with up to four hetero atoms, C_3-C_8 cycloalkanes that are optionally substituted with short-chain C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, amino, monosubstituted amino, and/or halogen groups, heterocyclic compounds with 3 to 6 ring atoms and up to four hetero atoms,
aromatic compounds with up to 8 ring atoms that are optionally substituted with cyano, hydroxy, short-chain C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, amino, monosubstituted amino, trihaloalkyl, and/or halogen groups, and heteroaryls with 3 to 7 ring atoms and up to four hetero atoms.

It is particularly preferred for the parent substance R to be selected from a single bond, methyl, ethane, ethene, ethyne, propane, isopropane, butane, isobutane, sec-butane, pentane, isopentane, neopentane, hexane, azine, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, pyrrole, pyrroline, pyrrolidine, imidazole, imidazoline, pyrazolidine, thiazole, thiazoline, thiazolidine, isothiazole, isothiazoline, isothiazolidine, benzothiazole, furan, dihydrofuran, tetrahydrofuran, benzofuran, thiophene, benzothiophene, oxazole, oxazoline, oxazolidine, benzoxazole, isoxazole, isoxazoline, isoxazolidine, piperidine, piperazine, pyrimidine, morpholine, dihydropyran, tetrahydropyran, pyridazine, benzene, furoxane, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, pyridine and its N-oxide, dihydropyridine, pyrimidine, or pyrazine. It is clear that the hetero atoms are positioned at any points in the ring.

It is also preferred for R_1 and R_2 independently of one another to be hydrogen atoms or a $-CONH_2$ residue.

Very particularly preferred are

2,6-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (6),

1,4-bis(1-aziridino-1-hydroxyiminomethyl)benzene (7),

1,4-di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)benzene (8),

1,3-bis(1-aziridino-1-hydroxyiminomethyl)benzene (9),

1,3,5-tris(1-aziridino-1-hydroxyiminomethyl)benzene (10),

1,3-di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)benzene (11),

2,6-di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)pyridine (12),

3,5-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (13),

2,5-bis(1-aziridino-1-hydroxyiminomethyl)pyridine ((14),

2,4-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (15),

2,5-bis(1-aziridino-1-hydroxyiminomethyl)furan (16),

3,4-bis[(aziridinyl)-1-hydroxyiminomethyl]furoxane (17),

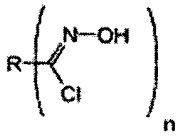
bis(2-methoxycarbonylaziridino)glyoxime (18),

bis(2-carbamoylaziridino)glyoxime (19),

2,2'-azinobis(1-aziridino-1-hydroxyiminomethyl)propane (20), and

2,2'-azinobis[1-(2-carbamoylaziridino)-1-hydroxyimino]propane (21).

Another subject of this invention is a method for preparing 1-aziridino-1-hydroxyiminomethyl derivatives pursuant to the invention, by reacting a halogen

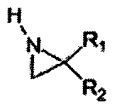


II

II

compound with the general formula II

wherein R and n have the meanings given above, in a known way with an aziridine derivative with the general formula III

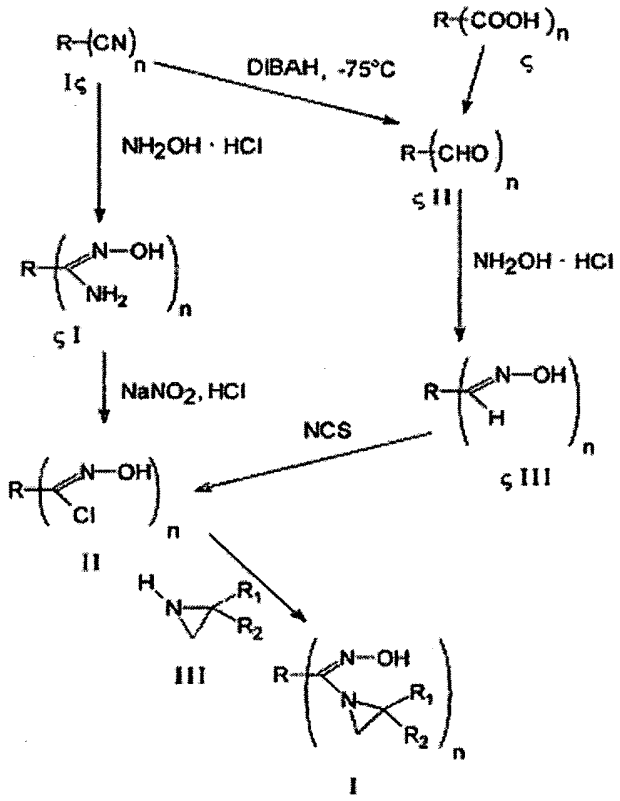


III

wherein R_1 and R_2 have the meanings given above.

The compounds of Formula I pursuant to the invention can be prepared by known methods according to the reaction diagram 1. To this end, nitriles with the general formula IV are converted to the carboxamide oximes with the general structure VI by reaction with hydroxylamine hydrochloride. By diazotization in hydrochloric acid medium, the chlorinated oximes of Structure II are obtained, which can then be converted to the compounds pursuant to the invention by reaction with aziridines of Formula III. Alternatively, as indicated in reaction diagram 1, the synthesis can be carried out starting with the carboxylic acids V by standard procedures described in the literature. The experimental method is indicated in the examples for the sequence IV → VI → II → I.

Reaction Diagram 1



Another subject of this invention is drugs characterized by containing a compound according to the general formula I.

Also a subject of this invention are drugs for oral, rectal, subcutaneous, intravenous, or intramuscular administration that contain a compound with the general formula I in addition to conventional vehicles and diluents.

Suitable dosage forms and their preparation are known for themselves and are described, for example in "Hagers Handbuch der pharmazeutischen Praxis" (*Hager's Manual of Pharmaceutical Practice*), Springer Verlag - Berlin - Heidelberg, 1991, Volume 2, pp. 622 ff.

The drugs of the invention are prepared by known methods with the customary solid or liquid vehicles or diluents and the pharmaceutical adjuvants customarily used for the desired method of administration, in suitable doses. The preferred preparations consist of a dosage form that is suitable for oral administration. Examples of such dosage forms are tablets, film-coated tablets, sugar-coated tablets, capsules, pills, powders, solutions or suspensions, or depot forms.

Of course parenteral preparations such as solutions for injection are also practical. Suppositories should also be mentioned as examples of preparations.

Appropriate tablets can be obtained, for example, by mixing the active ingredient with known adjuvants, for example, inert diluents such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, disintegrants such as corn starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talc, and/or agents for producing a depot effect such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets can also consist of several layers.

Correspondingly, sugar-coated tablets can be prepared by coating cores prepared similarly to the tablets with agents ordinarily used in coatings for sugar-coated tablets, for example polyvinylpyrrolidone or shellac, gum arabic, talc, titanium dioxide, or sugar. The shell of the sugar-coated tablet can also consist of several layers, for which the adjuvants mentioned above for tablets can be used.

Solutions or suspensions with the active ingredient pursuant to the invention can also contain, in addition, flavor-improving agents such as saccharin, cyclamate, or sugar, as well as flavorings such as vanillin or orange extract. The can also contain dispersants such as sodium carboxymethylcellulose or preservatives such as p-hydroxybenzoates. Capsules containing active ingredients can be prepared, for example, by encapsulating the active ingredient mixed with an inert carrier such as lactose or sorbitol in gelatin capsules.

Suitable suppositories can be prepared, for example, by mixing with vehicles intended for the purpose such as neutral fats or polyethylene glycol or their derivatives.

Of course transdermal therapeutic systems (TTSs) are also practical.

The compounds pursuant to the invention with the general formula I show antitumoral activity. The antitumoral activities of some compounds pursuant to the invention in the monolayer cytotoxicity test on selected cell lines are shown in

Table 1. The low susceptibility of fibroblasts and endothelial cells with the use of the compounds pursuant to the invention is surprising.

Another subject of this invention is therefore the use of the 1-aziridino-1-hydroxyiminomethyl derivatives with the general formula I for preparing drugs for the treatment of tumors or cancerous diseases.

However, the use of the 1-aziridino-1-hydroxyiminomethyl derivatives according to the general formula I for the treatment of tumors or of cancerous diseases is also a subject.

Another subject of this invention is the use of 1,1'-[1,2-bis(hydroxyimino)-1,2-ethanediyl]bisaziridine (1) to prepare drugs for the treatment of tumors or of cancerous diseases, and that of 1,1'-[1,2-bis(hydroxyimino)-1,2-ethanediyl]bisaziridine (1) for the treatment of tumors or of cancerous diseases.

Table 1:

Antitumoral activity of selected compounds pursuant to the invention

Substance IC_{50} [µg/ml]		1	6	14	7	9	10	16
Organ/cell line								
Colon	HT29	0.486	0.117	0.200	0.258	0.329	0.670	0.481
Stomach	GXF 251L	0.781	0.020	0.717	0.542	1.506	3.964	1.661
Lung	LXFL 529	0.441	0.027	0.006	0.038	0.063	0.100	0.099
Breast	401 NL	0.040	0.207	0.011	0.018	0.060	0.043	0.039
Kidney	944 LL	0.923	0.115	0.198	0.348	0.788	0.750	1.359
Uterus	1138 L	0.173	0.014	0.034	0.038	0.066	0.111	0.073

The mean IC_{50} values were determined for the compound 6 pursuant to the invention on a total of 12 cell lines (Table 3) compared to the therapy standard 5-fluorouracil (5FU) (See Table 2).

A clear superiority of the compound pursuant to the invention over the therapy standard is seen from these figures.

Table 2

Comparison of the antitumoral effect of (6) with the therapy standard 5-fluorouracil (5FU)

Compound	**IC_{50} [µg/ml]**
(6)	0.030
5FU	0.054

Table 3

Tumor cell lines used

Tumor	Cell line
Breast	MAXF 401NL
	MCF-7
Colon	HT29
Stomach	GXF251L
Lung	LXFA 629L
	LXFE66L
	LXFL529
Melanoma	MEXF 462NL
	MEXF 514L
Ovary	OVCAR3
Kidney	RXF 944L
Uterus	UXF 1138L

The following examples explain the invention.

Examples

Example 1

Preparation of 2,6-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (6)

Pyridine-2,6-di(carboxamide oxime)

To a solution of hydroxylamine hydrochloride (18.07 g; 26 mmol) and NaOH (10.40 g; 26 mmol) in H_2O (90 ml) is added dropwise with vigorous stirring a solution of pyridine-2,6-dicarbonitrile (12.9 g; 10 mmol) in ethanol (60 ml). An exothermic reaction occurs, and stirring is then continued for 1.5 h at 40-50 °C. After cooling, the precipitate is filtered off and washed with H_2O. Obtained after drying is 16.5 g (85% of the theoretical) of product. M.p. 237-239 °C. ^{1}H NMR. (DMSO-d_6: δ 6.20 (4H, s, NH_2); 7.76 (3H, s, C_5H_3N); 9.76 (2H, s, OH), -CHN (%) found: C 43.6; H 4.5; N 35.9 - calc.: C 43.1; H 4.6; N 35.9.

Pyridine-2,6-dihydroxamic [acid] dichloride

To a cooled solution of pyridine-2,6-di(carboxamide oxime) (1.95 g; 10 mmol) in dilute HCl (20 ml conc. HCl + 8 ml H_2O) is cautiously added dropwise with stirring a solution of $NaNO_2$ (1.78 g; 25 mmol) in H_2O (5 ml). After 1.5 h at 0-10 °C, the solution is stirred for 12 h longer at room temperature. The precipitate is then filtered off and washed with H_2O. Obtained after drying is 2.0 g (79% of the theoretical) of product. M.p. 168-170 °C (dec.), - ^{1}H NMR (DMSO-D_6): δ 8.00 (3H, s, C_5H_3N); 12.7 (2H, s, OH). - CHN (%) found C 33.7; H 2.2; N 16.6 - calc.: C 33.3; H 2.2; N 16.7.

2,6-Bis(1-aziridino-1-hydroxyiminomethyl)pyridine (6)

To a solution of aziridine (0.65 g; 15 mmol) and $N(C_2H_5)_3$ (2.0 g; 20 mmol) in acetonitrile (20 ml) cooled to 0 °C is added dropwise with stirring a suspension of pyridine-2,6-dihydroxamic acid dichloride (1.26 g; 5 mmol) in CH_3CN (20 ml). The mixture is stirred for 90 min and the precipitated triethylamine hydrochloride is filtered off. The filtrate is evaporated under vacuum, and ethyl acetate is added. The mixture is filtered again and the product is washed with $CHCl_3$. Obtained is 0.76 g (60% of the theoretical) of product. M.p. 194-196 °C (dec.). ^{1}H NMR: δ 2.31 (8H, s, CH_2); 7.73 (3H, s, C_5H_3N); 10.64 (2H, s, OH). CHN (%) found: C 52.4; H 5.3; N 27.5 ($C_{11}H_{13}N_5O_2$ x 0.25 H_2O) - calc.: C 52.5; H 5.4; N 27.8.

The following compounds are obtained by an analogous method:

Example 2

1,4-Bis(1-aziridino-1-hydroxyiminomethyl)benzene (7)

M.p. 220-222 °C (dec.). ^{1}H NMR: δ 2.20 (8H, s, CH_2); 7.00 (4H, s, C_6H_4); 12.6 (2H, s, OH). CHN (%) found: C 58.3; H 5.9: N 22.4 ($C_{12}H_{14}N_4O_2$) - calc.: C 58.5; H 5.7; N 22.7.

Example 3

1,4-Di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)benzene (8)

M.p. 248-250 °C (dec.). ^{1}H NMR: δ 2.36 (4H, s, CH_2); 2.82 (2H, m. CH); 7.16 and 7.47 (each 2H, s, s, NH_2); 7.64 (4H, s, C_6H_4); 10.6 (2H, s, OH). CHN (%) found: C 50.3; H 4.9; N 24.9 ($C_{14}H_{16}N_6O_4$) - calc. C 50.6; H 4.8; N 25.3.

Example 4

1,3-Bis(1-aziridino-1-hydroxyiminomethyl)benzene (9)

M.p. 179-181 °C (dec.). ^{1}H NMR: δ 2.17 (8H, s, CH_2); 7.31 (1H, t, C_6H); 7.62 (2H, d, C_6H_2); 8.11 (1H, s, C_6H); 11.3 (2H, s, OH). CHN (%) found: C 58.7; H 5.8; N 22.3 ($C_{12}H_{14}N_4O_2$) - calc.: C 58.5; H 5.7; N 22.7.

Example 5

1,3,5-Tris(1-aziridino-1-hydroxyiminomethyl)benzene (10)

M.p. >300 °C (dec.). ^{1}H NMR: δ 2.16 (12H, s, CH_2); 8.00 (3H, s, C_6H_3); 11.4 (3H, s, OH). CHN (%) found: C 54.1; H 5.4; N 25.0 ($C_{15}H_{18}N_6O_3$) - calc.: C 54.5; H 5.5; N 25.4.

Example 6

1,3-Di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)benzene (11)

M.p. 209-211 °C (dec.). ^{1}H NMR: δ 2.38 (4H, m, CH_2); 3.02 (2H, m, CH); 7.16 and 7.42 (each 2H, s, s, NH_2); 7.42 (1H, t, C_6H); 7.91 (1H, t, C_6H); 10.6 (2H, m, OH). CHN (%) found: C 45.9; H 5.3; N 22.8 ($C_{14}H_{16}N_6O_4$ x 2 H_2O) - calc.: C 45.6; H 5.5; N 22.8.

Example 7

2,6-Di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)pyridine (12)

M.p. 206-208 °C (dec.). ^{1}H NMR: δ 2.38 (4H, m, CH_2); 2.96 (2H, m, CH); 7.11 and 7.40 (each 2H, ss, NH_2); 7.76 (3H, s, C_5H_3N); 10.78 (2H, s, OH). CHN (%) found: C 46.6; H 4.6; N 29.0 ($C_{13}H_{15}N_7O_4$) - calc.: C 46.8; H 4.5; N 29.4.

Example 8

3,5-Bis(1-aziridino-1-hydroxyiminomethyl)pyridine) (13)

M.p. >300 °C (dec.). ^{1}H NMR: δ 2.27 (8H, s, CH_2); 8.29 (1H, t, 4-C_5HN); 8.78 (2H, d, 2,6-C_5H_2N); 11.7 (2H, s, OH). CHN (%) found: C 53.7; H 5.1; N 28.2 ($C_{11}H_{13}N_5O_2$) - calc.: C 53.4; H 5.3; N 28.3.

Example 9

2,5-Bis(1-aziridino-1-hydroxyiminomethyl)pyridine (14)

M.p. 190-192 °C (dec.). ^{1}H NMR: δ 2.22 (4H, s, CH_2); 2.26 (4H, s, CH_2); 7.76 (1H, d, C_5HN); 7.96 (1H, d, C_5HN); 8.78 (1H, s, C_5HN); 11.7 (2H, s, OH). CHN (%) found: C 53.8; H 5.2; N 28.0 ($C_{11}H_{13}N_5O_2$) - calc.: C 53.4; H 5.3; N 28.3.

Example 10

2,4-Bis(1-aziridino-1-hydroxyiminomethyl)pyridine (15)

M.p. >300 °C (dec.). ^{1}H NMR: δ 2.20 (8H, s, CH_2); 7.53 (1H, dd, C_5HN); 8.16 (1H, d, C_5HN); 8.51 (1H, d, C_5HN); 11.6 (1H, s, OH); 11.8 (1H, s, OH). CHN (%) found: C 53.4; H 5.5; N 28.0 ($C_{11}H_{13}N_5O_2$) - calc.: C 53.4; H 5.3; N 28.3.

Example 11

2,5-Bis(1-aziridino-1-hydroxyiminomethyl)furan (16)

M.p. 182-184 °C (dec.). ^{1}H NMR: δ 2.22 (8H, s, CH_2); 6.78 (2H, s, C_4H_2O); 10.5 (2H, s, OH). CHN (%) found: C 47.3; H 5.6; N 22.1 ($C_{10}H_{12}N_4O_4$) - calc.: C 47.2; H 5.6; N 22.0.

Example 12

3,4-Bis[(aziridinyl-1)hydroxyiminomethyl]furoxane (17)

M.p. >300 °C (dec.). ^{1}H NMR: δ 2.18 (4H, s, CH_2); 2.43 (4H, s, CH_2); 11.1 (1H, s, OH); 11.4 (1H, s, OH). CHN (%) found: C 38.2; H 4.2; N 32.9 ($C_8H_{10}N_6O_4$) - calc.: C 37.8; H 4.0; N 33.1.

Example 13

Bis(2-methoxycarbonylaziridino)glyoxime (18)

M.p. 212-214 °C. ^{1}H NMR: δ 2.36 (4H, m, CH_2); 2.96 (2H, m, CH); 3.62 (6H, s, CH_3); 10.71 (2H, s, OH). CHN (%) found: C 42.3; H 5.0; N 19.3 ($C_{10}H_{14}N_4O_6$) - calc.: C 42.0; H 4.9; N 19.6.

Example 14

Bis(2-carbamoylaziridino)glyoxime (19)

M.p. >300 °C. ^{1}H NMR: δ 2.28 (1H, m, CH); 2.40 (1H, m, CH); 2.83 (1H, m, CH); 7.09 and 7.24 (each 1H, s, s, NH_2); 10.65 (1H, s, OH). CHN (%) found: C 37.1; H 4.8; N 32.1 ($C_8H_{12}N_6O_4$) - calc.: C 37.5; H 4.7; N 32.8.

Example 15

2,2'-Azinobis(1-aziridino-1-hydroxyimino)propane (20)

M.p. 172-174 °C. ^{1}H NMR: δ 1.91 (6H, s, CH_3); 2.20 (8H, s, CH_2); 10.9 (2H, s, OH). CHN (%) found: C 46.4; H 4.5; N 32.2 ($C_{10}H_{16}N_6O_2$ x 0.5 H_2O) - calc.: C 46.0; H 6.6; N 32.2.

Example 16

2,2'-Azinobis[1-(2-carbamoylaziridino)-1-hydroxyimino]propane (21)

M.p. 242-244 °C (dec.). ^{1}H NMR: δ 1.98 (6H, s, CH_3); 2.53 (2H, s, CH_2); 2.53 (2H, m, CH_2); 2.89 (2H, m, CH); 7.04 and 7.22 (each 2H, ss, NH_2); 11.02 (2H, s, OH). CHN (%) found: C 41.6; H 5.4; N 32.1 ($C_{12}H_{18}N_8O_4$ x 0.5 H_2O) - calc.: C 41.5; H 5.5; N 32.3.

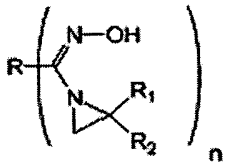
Example 19 [*sic*]

To test the antiproliferative properties of the compounds pursuant to the invention, a modified propidium iodide assay (Dengler, W.A., Schulte, J., Berger, P.B., Mertelsmann, R., Fiebig, H. H.: Anti-Cancer Drugs 6, 522-532, (1995)) was carried out as described below:

Tumor cells from cell cultures in the exponential growth phase (RPMI Medium, 10% FCS) were harvested, counted, and transferred into 96-well microtiter plates (140 µL cell suspension, 1×10^5 or 5×10^4 cells/mL). After a period of 24 h in which the cells resumed their exponential growth, 10 µL of the test substance dissolved in medium was added to each well (each test concentration was determined in triplicate). After 3-6 days of incubation (depending on the rate of cell doubling), the culture medium was replaced by 200 µL of a fresh medium that contained propidium iodide (25 µg/mL). The microtiter plates were then kept for 24 hours at -18 °C to achieve total cell death. After thawing the plates, fluorescence was measured by means of a Millipore Cytofluor 235 (excitation 530 nm, emission 620 nm). The IC_{50} values of the test compounds were calculated according to the published formula. If an IC_{50} could not be determined within the tested dosage units, the lowest or highest concentration tested was used in each case for the calculation.

Patent Claims

1. 1-Aziridino-1-hydroxyiminomethyl derivatives with the general formula I



I

wherein

R stands for any organic residue that is able to bond covalently two aziridine oxime groups,

R_1 and R_2 independently of one another stand for a hydrogen atom or a $-CH_3$, $-C_2H_5$, -CN, -COOH, $-COOCH_3$, $-COOC_2H_5$, $-CONH_2$, or $-C_6H_5$ group, and

n is the whole number 2.

2. 1-Aziridino-1-hydroxyiminomethyl derivatives pursuant to claim 1, characterized by the fact that R is any organic residue that is selected from

a single bond, linear or branched, saturated or unsaturated alkanes or heteroalkanes with up to 6 carbon atoms and with up to four hetero atoms, C_3-C_8 cycloalkanes that are optionally substituted with short-chain C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, amino, monosubstituted amino, and/or halogen groups,

heterocyclic compounds with 3 to 6 ring atoms and up to four hetero atoms,

aromatic compounds with up to 8 ring atoms that are optionally substituted with cyano, hydroxy, short-chain C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, amino, monosubstituted amino, trihaloalkyl, and/or halogen groups, and

heteroaryls with 3 to 7 ring atoms and up to four hetero atoms.

3. 1-Aziridino-1-hydroxyiminomethyl derivatives pursuant to claim 2, characterized by the fact that the parent substance R is selected from a single bond, methyl, ethane, ethene, ethyne, propane, isopropane, butane, isobutane, sec-butane, pentane, isopentane, neopentane, hexane, azine, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, pyrrole, pyrroline, pyrrolidine, imidazole, imidazoline, pyrazolidine, thiazole, thiazoline, thiazolidine, isothiazole, isothiazoline, isothiazolidine, benzothiazole, furan, dihydrofuran, tetrahydrofuran, benzofuran, thiophene, benzothiophene, oxazole, oxazoline, oxazolidine, benzoxazole, isoxazole, isoxazoline, isoxazolidine, piperidine, piperazine, pyrimidine, morpholine, dihydropyran, tetrahydropyran,

pyridazine, benzene, furoxane, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, pyridine and its N-oxide, dihydropyridine, pyrimidine, or pyrazine.

4. 1-Aziridine-1-hydroxyiminomethyl derivatives pursuant to one of the preceding claims, characterized by the fact that R_1 and R_2 independently of one another represent hydrogen atoms or a -$CONH_2$ group.

5. 1-Aziridino-1-hydroxyiminomethyl derivatives pursuant to claim 1, namely

2,6-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (6),

1,4-bis(1-aziridino-1-hydroxyiminomethyl)benzene (7),

1,4-di(α-2-carbomoylaziridino-α-hydroxyiminomethyl)benzene (8),

1,3-bis(1-aziridino-1-hydroxyiminomethyl)benzene (9),

1,3,5-tris(1-aziridino-1-hydroxyiminomethyl)benzene (10),

1,3-di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)benzene (11),

2,6-di(α-2-carbamoylaziridino-α-hydroxyiminomethyl)pyridine (12),

3,5-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (13),

2,5-bis(1-aziridino-1-hydroxyiminomethyl)pyridine ((14),

2,4-bis(1-aziridino-1-hydroxyiminomethyl)pyridine (15),

2,5-bis(1-aziridino-1-hydroxyiminomethyl)furan (16),

3,4-bis[(aziridinyl)-1-hydroxyiminomethyl]furoxane (17),

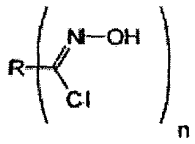
bis(2-methoxycarbonylaziridino)glyoxime (18),

bis(2-carbamoylaziridino)glyoxime (19),

2,2'-azinobis(1-aziridino-1-hydroxyiminomethyl)propane (20), and

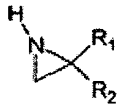
2,2'-azinobis[1-(2-carbamoylaziridino)-1-hydroxyimino]propane (21).

6. A method for preparing 1-aziridino-1-hydroxyiminomethyl derivatives pursuant to claim 1, in which a halogen compound with the general formula II



II

wherein R and n have the meanings given in claim 1, is reacted with an aziridine derivative with the general formula III



III

wherein R_1 and R_2 have the meanings given in Claim 1.

7. A drug, characterized by the fact that it contains a compound pursuant to one of the claims 1 to 6.

8. Use of the 1-aziridino-1-hydroxymethyl derivatives pursuant to claim 1 to prepare drugs for the treatment of tumors or cancerous diseases.

9. Use of the 1-aziridino-1-hydroxymethyl derivatives pursuant to claim 1 for the treatment of tumors or cancerous diseases.

10. Use of 1,1'-[1,2-bis(hydroxyimino)-1,2-ethanediyl]bisaziridine for the preparation of drugs for the treatment of tumors or cancerous diseases.

11. Use of 1,1'-[1,2-bis(hydroxyimino)-1,2-ethanediyl]bisaziridine for the treatment of tumors or cancerous diseases.

Abstract: Described are new 1-aziridino-1-hydroxyiminomethyl derivatives with the general formula (I), wherein R indicates any organic residue which is able to covalently bond two aziridine oxime groups, R_1 and R_2 independently of one another stand for a hydrogen atom or a $-CH_3$, $-C_2H_5$, -CN. -COOH, $-COOCH_3$, $-COOC_2H_5$, $-CONH_2$, or $-C_6H_5$ group, and n is the whole number 2, as well as a method for their preparation and drugs containing these compounds. The compounds of general formula (I) show antitumoral action.

Attorney Docket No. 81847

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled 1-AZIRIDINO-1-HYDROXYIMINOMETHYL-DERIVATE, VERFAHREN ZU DEREN HERSTELLUNG UND DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL, the specification of which: (check one)

[ ] is attached hereto.
[X] was filed as PCT Application No. PCT/DE00/03441 on September 22, 2000, and has been assigned U.S. Patent Application Serial No. 10/089,039.
[ ] was filed on
and assigned Serial No.:
and was amended on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed:

Prior Foreign/PCT Application(s)			Priority Claimed
199 47 440.0	Germany	24 September 1999	[X] yes [ ] no
(number)	(country)	(day/month/year filed)	
			[ ] yes [ ] no
(number)	(country)	(day/month/year filed)	

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	FILING DATE:

81847

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or under Title 35, United States Code, § 365(c) of any PCT international application designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(application number)	(filing date)	(Status - patented, pending, abandoned)
(application number)	(filing date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Irving M. Kriegsman, Esq., Reg. No. ~~22,733~~; Edward M. Kriegsman, Esq., Reg. No. 33,529; and Daniel S. Kriegsman, Esq., Reg. No. 40,057. (3)

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I hereby declare that all statements made herein of my own knowledge are true and that any statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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